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10/754,711	01/12/2004	Deborah Kim Glencross	025455-113	1340

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/754,711	GLENCROSS, DEBORAH KIM	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 6-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/12/04 and 6/14/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

8-0-0

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1, 2 and 5, in the reply filed on 9 May 2005 is acknowledged. The traversal is on the ground(s) that the methods of claims 3, 4 and 12 have been amended to be dependent on the method of claim 1; additionally claim 1 has been included to include all subsets of CD4 cells. Furthermore, the method steps of claims 3 and 4 are now additional/further steps to those set forth in claim 1, as such the method steps of claims 3 and 4 cannot be performed until the method of claim 1 is carried out. Still further, claim 12 falls within the scope of claim 1 because it depends from claim 1 and further discloses subsets of cells enumerated in claim 1. Finally, applicant argues that regardless of whether the groups are independent and/or distinct searching all five inventions in a single application would not impose a serious burden on the examiner. These arguments are not found persuasive because the method of claim 1 is still distinct from the method of claims 3 and 4, and the method of claim 1 is still directed to a different population then that of claims 12 and 13, and searching five independent and distinct inventions in a single application is a serious burden.

Steps (e)-(g) of claim 3 (Group 2) do not require all the steps of claim 1 (Group 1), but only require claim 1 step (a), identifying the total CD45 expressing population as a reference population. Steps (b)-(d) of claim 1 rely on measuring cell populations based on the presence of the CD4 protein marker on the select cell populations. Steps (e)-(g) of claim 3 do not appear to measure monocyte, eosinophil or granulocyte populations based on the presence of the CD4 protein, rather the steps (e)-(g) of claim 3 require the target cells to be CD4 negative; therefore another marker must be relied on to separate these target cell populations. Therefore the methods of claims 1 and 3 isolate different populations of cells based on different cell protein markers; while both share the initial step of identifying the total CD45 expressing population as a reference, this generic step is not sufficient to make the methods co-extensive.

Because the method of claim 1 is based on identifying cells based on the presence of CD4 protein, specific parameters, antibodies and selection methods are required that are specific for CD4 protein. Alternatively, the methods of claim 3 require identifying cells that lack the CD4 protein marker, therefore other, distinct marker proteins must be identified and different antibodies or selection methods must be utilized to separate these particular cell populations. Thus, because the methods rely on different markers and different selection methods, and have different effects of separating very different populations of cells, the methods remain distinct.

The methods of groups 1 (claim 1) and 5 (claim 12) remain distinct because, though the method of claim 12 has been amended to be dependent on claim 1, the methods are still directed to different populations and are thus distinct. The method of claim 1 can be performed on any blood cell sample from the general population; however the method of claim 5 is restricted to only the population comprising patients with HIV or another immune deficiency condition. Though patients with HIV or another immune deficiency condition or disease are part of the general population, methods directed to this specific population require special modifications and considerations that merit it a distinct method.

With regards to applicant's argument that searching of all inventions in one application would not result in a serious burden on the examiner, the examiner maintains that searching of five independent and distinct inventions, each within a different classification, would, in fact, constitute serious burden on the examiner. Burden consists not only of specific searching of classes and subclasses, but also of searching multiple databases for foreign references and literature searches. Burden also resides in the examination of independent claim sets for clarity, enablement and double patenting issues. Therefore searching the instant five patentably distinct inventions would, in fact, impose a serious burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL. Claims 1, 2 and 5 will be examined for patentability. Claims 1-13 remain pending in the current application, with 3, 4 and 6-13 withdrawn from consideration.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: ENUMERATION OF CD4+ CELLS BY A DUAL PLATFORM METHOD.

Priority

Acknowledgment is made of applicant's claim for priority as a continuation of PCT/IB/02/02725 filed on 11 July 2002, which further claims priority to South African application 2001/5700, filed on 11 July 2001.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and dependent claims 2 and 5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claim 1 is directed to a method for enumerating the number of CD4 cells or subset thereof in a cell sample, the method comprising the steps of: a) identifying the total CD45 expressing population as a reference population; b) determining the percentage of CD4 [positive] lymphocytes or subset thereof as a function of the total CD45 [expressing] reference population identified in step (a); c) determining the number of CD4 [positive] cells per volume of blood; and d) calculating the number of

CD4 [positive] cells or subset thereof in the sample by multiplying the percentage of CD4 [positive] cells, obtained in step (b), by the CD 45 [expressing cell] count obtained in step (c).

First, the claim references CD4 cells and CD4 lymphocytes (lines 1-2, 4, 5, 8, and 9) and CD45 cells (lines 6, 7 & 10); these are inappropriate terms. CD4 and CD45 are surface marker proteins; the certain cells express the CD4 or CD45 protein markers are referred to as CD4 or CD45 positive cells. The term 'CD45 expressing cells' is suitable; however CD 45 reference population is not, again the cells are CD45 positive cells or CD45 positive reference population.

Second, the preamble and step (d) refer to CD4 [positive] cells or a subset thereof; however, steps (a) and (b) refer to CD4 [positive] lymphocytes or subsets thereof. Lymphocytes are one type of CD4 positive cells, but other non-lymphocyte cells are also CD4 positive including monocytes/macrophages and eosinophils (See Nestor, Jr. et al, Pg. 1, paragraph 0008 & Pg. 2, paragraph 0010; Stewart et al, Pg. 3777, col. 1 & Table 1; Center et al, Pg. 167, col. 1 & Pg. 168, col. 1). Thus the claim appears to switch back and forth between a broad limitation (CD4 positive cells) and a narrow limitation (CD4 positive lymphocytes), See MPEP § 2173.05 (c). The metes and bounds of the claim cannot be determined because applicant switches back and forth between referencing CD4 positive cells, in general, and CD4 positive lymphocytes, specifically. From the specification it appears applicant is intending to enumerate the CD4 positive T-cell lymphocyte population; however, the current claim is directed to a method of enumerating all CD4 positive cells in a blood sample. Furthermore, it is not clear what cells are included in "subsets thereof" of CD4 [positive] lymphocytes or what cells are included in the "subsets thereof" of CD4 [positive] cells.

Third, there is insufficient antecedent basis for the limitation "the percentage of CD 4 [positive] cells or subset thereof" in the ninth line of claim 1. Specifically, step (b) references CD4 [positive] lymphocytes, which is not equal to the number of CD4 positive cells.

Fourth there is insufficient antecedent basis for the limitation "the CD 45 count obtained in step (c)" in the tenth line of claim 1. This portion of step (d) appears to reference the CD 45 [positive] cell count obtained in step (c); "CD45 count" as recited in step (d) refers to the number of CD45 proteins, not the number of CD45 positive cells.

Fifth, the preamble does not seem to properly correlate with the claims. The preamble is directed to a method of enumerating the number of CD4 [positive] cells in a cell sample; however, the steps in the method, particularly steps (a)-(b), are drawn to a method for measuring CD4 [positive] lymphocytes. CD4 positive cells include CD4+ T-cell lymphocytes as well as other non-lymphocytes cell, such as granulocytes and eosinophils; therefore, by identifying all CD4 positive cells in a whole blood sample, one will not obtain an accurate count of CD4+ T-cells, but a count of all CD4 positive cells in the sample.

Sixth, it is not clear how steps (a) and (c) differ. Both steps require determination of the total CD 45+ cell count.

Applicant's claim 2 requires the number of CD45 cells per volume of blood to be determined by either a single platform method or by a dual platform method using a white blood cell count obtained from a hematology analyzer.

First, as above, CD45 cells is not an appropriate term; CD45 expressing cells or CD45 positive cells is correct.

Second, it is not clear how a dual platform method, using a white blood cell count obtained from a hematology analyzer, is used to count the number of CD45 cells. The white blood cell count would be obtained by using the hematology analyzer alone. The hematology analyzer is the first "platform" of the dual platform method; the second "platform" would not accomplish the task of counting CD45 positive cells, which is the purpose of the method as defined by the preamble. Rather, a dual platform method would be used to count a subset of the CD45 expressing cells, such as CD4 positive cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Melnicoff et al (US Patent 5,385,822), in light of Dorland's Illustrated Medical Dictionary, 2005.

The claims are directed to a method for enumerating the number of CD4 cells or subset thereof in a cell sample, the method comprising the steps of: a) identifying the total CD45 expressing population as a reference population; b) determining the percentage of CD4 positive lymphocytes or subset thereof as a function of the total CD45 expressing reference population identified in step (a); c) determining the number of CD4 positive cells per volume of blood; and d) calculating the number of CD4 positive cells or subset thereof in the sample by multiplying the percentage of CD4 positive cells, obtained in step (b), by the CD 45 expressing cell count obtained in step (c).

Melnicoff et al teach a method of enumerating the number of CD4+ lymphocytes in a blood cell sample, comprising identifying the total leukocyte population on a Coulter counter, to be used as a reference population; followed by labeling the cell samples with fluorescent markers against CD4 and CD45; then performing flow cytometry to determine the percent of leukocytes (CD45+) that were CD4+ lymphocytes; the percent CD4+ lymphocytes was then multiplied by the leukocyte count to determine the number of CD4+ lymphocytes/mm^3 blood (See col. 19, ln 15-col. 21, ln 50; especially Ex. 3a steps 7-8 & 16-17 and Ex/ 3c step 11) (Claim 1).

Melnicoff et al initially count the number of leukocytes (CD45+) cells by means of a Coulter counter (See Col. 19, ln 51-52); a Coulter counter is a type of hematology analyzer that can be used to

count the number of formed elements (such as leukocytes) in a cubic millimeter of blood (See Dorland's Medical Dictionary). Other equivalent hematology analyzers include hemacytometers and automated counters such as flow cytometers (See Dorland's) (Claim 2). The method of Melnicoff et al can be considered a dual platform method, wherein the first 'platform' consists of the Coulter counter (hematology analyzer) and the second method consists of the flow cytometry analysis. Therefore the reference anticipates the claimed subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Melnicoff et al (US Patent 5,385,822), in view of Brando et al (Cytometry, 2000).

The claims are directed to a method for enumerating the number of CD4 cells or subset thereof in a cell sample, the method comprising the steps of: a) identifying the total CD45 expressing population as a reference population; b) determining the percentage of CD4 positive lymphocytes or subset thereof as a function of the total CD45 expressing reference population identified in step (a); c) determining the number of CD4 positive cells per volume of blood; and d) calculating the number of CD4 positive cells or subset thereof in the sample by multiplying the percentage of CD4 positive cells, obtained in step (b), by the CD 45 expressing cell count obtained in step (c).

Melnicoff et al teach a method of enumerating the number of CD4+ lymphocytes in a blood cell sample, comprising identifying the total leukocyte population on a Coulter counter, to be used as a reference population; followed by labeling the cell samples with fluorescent markers against CD4 and

CD45; then performing flow cytometry to determine the percent of leukocytes (CD45+) that were CD4+ lymphocytes; the percent CD4+ lymphocytes was then multiplied by the leukocyte count to determine the number of CD4+ lymphocytes/mm^3 blood (See col. 19, ln 15-col. 21, ln 50; especially Ex. 3a steps 7-8 & 16-17 and Ex/ 3c step 11).

Additionally, though Melnicoff et al initially count the number of leukocytes (CD 45+ cells) by means of a Coulter counter it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use microbead-based technologies to count the number of leukocytes per volume of blood (See Brando et al, Pg. 334, col. 2- Pg. 335, col. 2) (Claim 2).

It would further have been obvious to one of ordinary skill in the art to use any available blood sample to perform the analysis, including whole unlysed blood, unfractionated, fractionated or lysed whole blood (Claim 5). One of ordinary skill in the art would have been motivated to use any type of blood sample provided to perform the analysis because only the white blood cells are needed in the method. One of ordinary skill in the art would be motivated to use any type of blood sample in order to test the blood to monitor the progression of HIV in infected patients. Fractionating or lysing the blood sample would not affect the number of white blood cells or the CD4 or CD45 protein markers on the cells; therefore, one would expect success using any type of blood sample, based on what type of sample was provided, because a skilled technician would be able to identify and isolate the white blood cells from any type of blood sample and perform the method of Melnicoff et al.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brando et al (Cytometry, 2000), in view of Barnett et al (British Journal of Haematology, 1999).

The claims are directed to a method for enumerating the number of CD4 cells or subset thereof in a cell sample, the method comprising the steps of: a) identifying the total CD45 expressing population as a reference population; b) determining the percentage of CD4 positive lymphocytes or subset thereof as a function of the total CD45 expressing reference population identified in step (a); c) determining the number of CD4 positive cells per volume of blood; and d) calculating the number of CD4 positive cells or subset thereof in the sample by multiplying the percentage of CD4 positive cells, obtained in step (b), by the CD 45 expressing cell count obtained in step (c).

Brando et al teach a dual platform method for enumerating the number of cells in a given cell subset, comprising using a hematology analyzer to determine the number of reference cells per volume of sample to obtain an absolute cell count of a reference cell population; utilizing flow cytometry to determine the percentage of cells of the chosen cell subset in a reference sample (% cells of interest/reference sample); and then calculating the absolute cell count of the given cell subset as a function of the absolute cell count of the reference population (absolute cell count of cells of interest = (% of cells of interest/100%) x absolute cell count of reference cell population). Brando et al teach the total leukocyte population can be used as the reference population; the pan-leukocyte CD45 marker can be used in the gating strategy to encompass all leukocytes (Se pg. 329, col. 2- Pg. 330, col. 2). Though Brando et al do not provide an example wherein CD4+ cells are the given cell subset in the dual platform method, they do exemplify CD4+ cells as the cell subset of interest in the single platform technique example. Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made to enumerate CD4+ cells from a blood sample (as the given cell subset) in the method of Brando et al, wherein the total leukocyte population is used as the reference population (Claim 1). One of ordinary skill in the art would have been motivated to enumerate the number of CD4+ cells in a blood sample as a means for staging HIV-infected patients and monitoring the progression of the disease (See Pg. 328, col. 1). One would have expected success enumerating the number of CD4+ cells as the given

cell subset in the dual platform method of Brando et al because enumeration of CD4+ cells by flow cytometry is well known and commonly practiced in the art; Brando et al do not alter the flow cytometry aspect of the method, but only provide teachings on using leukocytes as the reference cell population (See Pg. 330, col. 1).

Brando et al teach that the absolute cell count of the reference population can be obtained from the number of reference cells per volume of sample on a hematology analyzer (See pg. 329, col. 2-Pg. 330, col. 1); however they also teach that the number of cells per volume of sample can be obtained by microbead-based technologies. In microbead-based technologies known amounts of fluorescent microbeads are admixed with a known volume of stained blood in a lyse-no-wash technique and the beads are counted along with the cells, thus the number of cells per volume is obtained (See Pg. 334, col. 2). Therefore it would have been obvious to one of ordinary skill in the art to use either a hematology analyzer or microbead-based technologies to calculate the number of leukocyte reference cells in a sample (Claim 2). One of ordinary skill in the art would have been motivated to use microbead-based technologies to obtain a reference cell count in order to eliminate errors due to variance between hematology analyzer technicians, as hematology analysis is performed by technicians and thus is subject to human error and variation between technicians' skill level (See Brando Pg. 330, col. 1 & Barnett et al, Pg. 1059, col. 1). One would have expected success using either cell counting method to obtain the absolute cell count of the reference cell population because Brando et al teach that both hematology analyzer and microbead-based technologies are acceptable cell counting methods.

It would further have been obvious to one of ordinary skill in the art to use any available blood sample to perform the analysis, including whole unlysed blood, unfractionated, fractionated or lysed whole blood (Claim 5). One of ordinary skill in the art would have been motivated to use any type of blood sample provided to perform the analysis because only the white blood cells are needed in the method. One of ordinary skill in the art would be motivated to use any type of blood sample in order to

test the blood to monitor the progression of HIV in infected patients. Fractionating or lysing the blood sample would not affect the number of white blood cells or the CD4 or CD45 protein markers on the cells; therefore, one would expect success using any type of blood sample, based on what type of sample was provided, because a skilled technician would be able to identify and isolate the white blood cells from any type of blood sample and perform the method of Brando et al.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651

LEON B. LANKFORD, JR.
PRIMARY EXAMINER